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α-Methyl phenylglycines by asymmetric α-arylation of alanine and their effect on the conformational preference of helical Aib foldamers

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α-Arylated alanine derivatives were made enantioselectively by migratory rearrangement of a urea derivative using (*R,R*)-pseudoephedrine as a chiral auxiliary. Incorporation of a single residue of the product α-methyl phenylglycine into an otherwise achiral oligomer of aminoisobutyric acid oligomer induced a preferred screw sense, detectable by a NMR reporter located at the remote terminus of the oligomer. The magnitude of the screw sense induction was greater when the chiral residue was located at the N-terminus of the foldamer, and in some cases the sense of induction was opposite to that of related α-methylated amino acids with α-substituents other than aryl.

Incorporation of an additional substituent at the α position of a typical proteinogenic amino acid has important consequences for the properties of the resulting quaternary amino acid. Several families of fungal non-ribosomal peptides incorporate quaternary amino acids into their type sequence. The most common of these is the achiral residue α-aminoisobutyric acid (Aib),[1] but also prevalent are the dialkylated chiral residues as isovaline, α-methylvaline, and α-methyl phenylalanine. These quaternary amino acid residues typically induce a strong preference for helical conformations, and extensive conformational studies have been carried out on peptides containing such residues.[2]

α-Methyl phenylglycine ((αMe)Phg) and its derivatives have been studied over the last two decades in programs involving peptide conformation and catalysis,[3] as resolving agents in resolutions through selective crystallization[4] or as alternative sweeteners.[5] Its derivatives are also found as a structural feature in many targets of medicinal chemistry (Figure 1),[6] making effective methods for its synthesis particularly valuable.

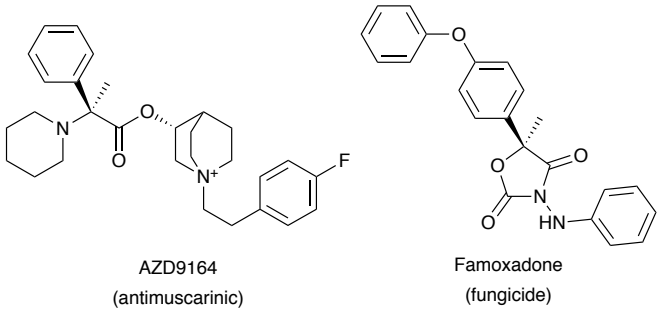

Figure 1: Examples of bioactive α-methyl phenylglycine derivatives.

In general, quaternary amino acids have been synthesised by alkylation of their naturally occurring tertiary parent, with the configuration of the product being controlled either by some form of chiral memory or by an asymmetric alkylation step.[7] The corresponding introduction of an aryl substituent is a much more challenging prospect. We have shown that *N*'-aryl urea derivatives of amino acids undergo rearrangements that yield hydantoin derivatives of quaternary amino acids bearing an α aryl substituent,[8] and Kawabata *et al.* concurrently reported a related reaction that allows incorporation of aryl substituents with chiral memory.[9] More recently, we reported a general approach to the stereoselective arylation of α-amino acids using pseudoephedrine as a chiral auxiliary.[10] This rearrangement was facilitated by temporary *in situ* protection of the urea as its *N*- or *O*-silyl derivative by treatment with trimethylsilyl chloride.

We now report that it is possible to synthesise enantio-enriched α-methyl phenylglycine derivatives by a practical modification of this rearrangement method, in which a 2,4-dimethoxybenzyl (DMB) group is used for protection of the urea *N* atom. We show that the resulting quaternary amino acid may be incorporated into a helical Aib-containing oligomer at either the C- or the N-terminus, and that the stereogenic centre of this single quaternary residue may

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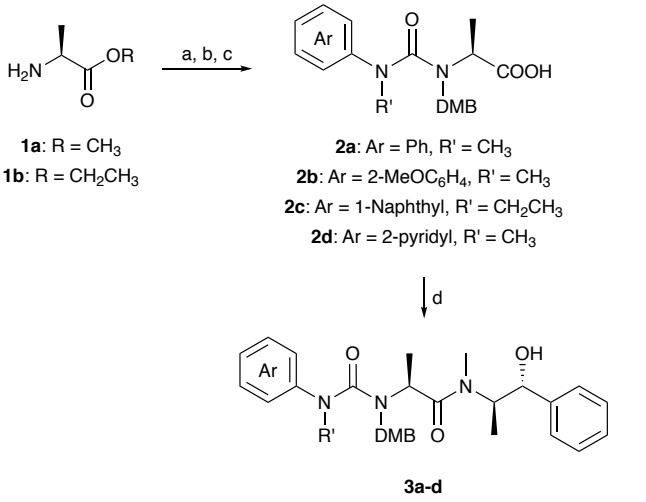
induces a screw sense preference in the whole of the resulting helical oligomer.

Results and Discussion

Enantioselective α-arylation of alanine

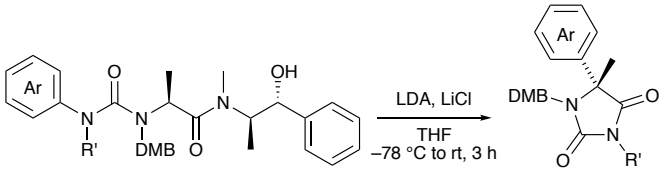
Starting materials **3a-d** for stereoselective rearrangement were made straightforwardly from alanine derivatives in four steps (Scheme 1). *N*-protection of alanine esters **1** with the 2,4-dimethoxybenzyl (DMB) group was achieved by reductive amination with 2,4-dimethoxybenzaldehyde. Coupling of the amine with a series of carbamoyl chlorides, followed by hydrolysis of the ester moiety with lithium hydroxide in a biphasic system, afforded carboxyureas **2a-d** in excellent yields. These carboxylic acids were coupled to (*R,R*)-pseudoephedrine without epimerisation using standard coupling reagents EDC.HCl and HOBt.H_2O to give **3a-d** in excellent overall yield.

The reaction conditions for stereoselective arylation were optimised by exploring base-promoted phenyl migration within compound **3a**. Optimal conditions were found to require an excess of lithium diisopropylamide (LDA) in THF in the presence of ten equivalents of lithium chloride. Full conversion was attained after deprotonation at –78 °C followed by a period of three hours at room temperature. As observed previously by IR,[8] enolate formation is followed by migration of the ring to the α position of the alanine residue, followed by cyclisation to the hydantoin with concurrent expulsion of the pseudoephedrine auxiliary. *N*-to-*C* migration of a selection of aryl rings was performed in moderate to good yield (Table 1), with enantiomeric excesses ranging from near-racemic (compound **4c**) to complete enantiopurity (compound **4a**). The reason for the strong variation in stereoselectivity with migrating ring is unclear, and shows that an alternative more general method is required for rings other than phenyl.[11]



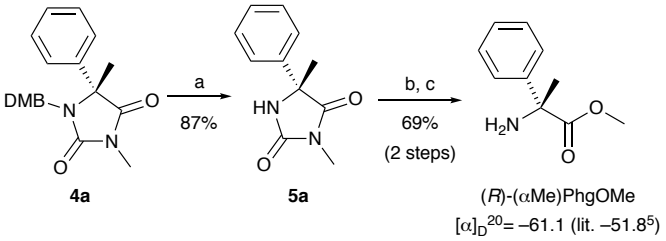
Scheme 1: Reagents and conditions: (a) 2,6-dimethoxybenzaldehyde, NaOAc, $NaHB(OAc)_3$, EtOH, rt; (b) ArN(R')COCl, triethylamine, MeCN, reflux; (c) LiOH, THF/H_2O, 45°C; (d) EDC.HCl, HOBt.H_2O, (*R,R*)-pseudoephedrine, CH_2Cl_2, rt. DMB = 2,4-dimethoxybenzyl.

Table 1: Stereoelective rearrangement of the pseudoephedrine derived compounds



3a-d 4a-d

Entry	Product	Ar	R'	Yield	e.r
1	4a	Ph	CH_3	69%	>99:1
2	4b	2-$MeOC_6H_4$	CH_3	56%	69:31
3	4c	Naphthyl	CH_2CH_3	58%	55:45
4	4d	2-pyridyl	CH_3	37%	78:22



Scheme 2: Hydrolysis of the hydantoin. Reagents and conditions: (a) TfOH, TFA, 0°C; (b) NaOH, H_2O, dioxane, 100°C; (c) $SOCl_2$, MeOH, rt. DMB = 2,4-dimethoxybenzyl.

Enantiopure hydantoin **4a** was converted into the corresponding amino acid methyl ester (Scheme 2). Acidic removal of the dimethoxybenzyl group afforded free hydantoin **5a**, which was hydrolysed under basic conditions to α-methyl phenylglycine, isolated as its methyl ester. Comparison of the optical rotation with reported values allowed us to assign the stereochemistry at the quaternary carbon to be *R*.[5] Interestingly, the stereocenter formed in this rearrangement is the opposite of the major enantiomer formed in our previous, protecting group-free, rearrangement using the same enantiomer of pseudoephedrine.[10] Deprotection of hydantoin **4b** followed by hydrolysis gave only the corresponding amino *N*-methyl amide **6b** despite forcing conditions (See the Supporting Information for details), suggesting that additional substitution not only decreases stereoselectivity but also hinders significantly the hydrolysis of the products.

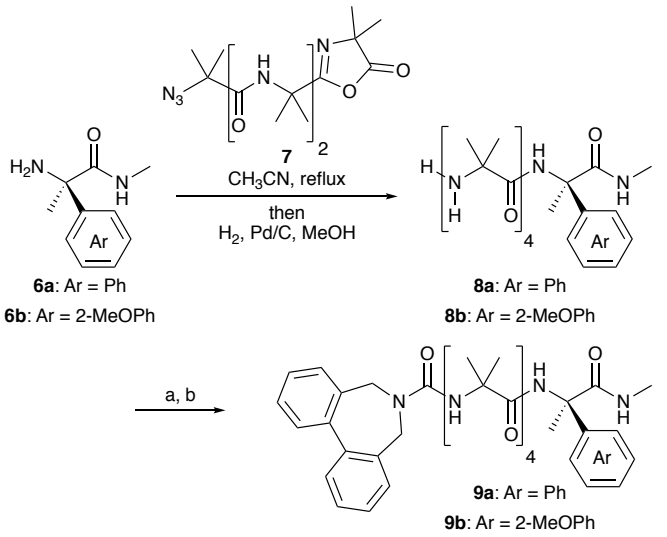
Synthesis and conformation of foldamers containing an α-aryl quaternary amino acid residue

Homo-oligomers of the achiral quaternary amino acid Aib form 3_{10} helices as an interconverting mixture of *M* and *P* enantiomeric conformers, but even a single chiral amino acid can powerfully bias the *M*:*P* ratio, with the absolute screw sense induction depending on the nature and location of the chiral residue.[12] No information is available on the influence of α-arylated residues on screw sense preference, so the chiral quaternary amino acid derivatives previously made were coupled to achiral Aib oligomers at either the N- or the C-

terminus and their conformational influence was explored by NMR and by Circular Dichroism (CD).

(αMe)PhgOMe was converted to its *N*-methyl amide derivative **6a** (See SI for details) and, together with its *ortho*-methoxylated analogue **6b,** coupled to the C-terminus of an Aib tetramer by nucleophilic attack on the foldamer's azlactone derivative **7** (Scheme 3). In order to monitor the global screw sense preference of the resulting foldamer, the tetramer was coupled to a N-terminal azepine probe.[12b,13] Hydrogenation of the N-terminal azide allowed introduction of the probe in good yield by acylation with its succinimidyl ester derivative.

Addition of DMSO-*d*6 to a solution of **9a** in CD_2Cl_2/CD_3OH 9:1 led to a significant deshielding of the two highest field N-H protons (Figure 2). This downfield shift suggests that the two NH protons furthest from the controller in **9a** are not part of a hydrogen-bonding network, consistent with the adoption of a 3_{10}-helical conformation. Further support for this interpretation was gained from the CH–NH regions of the ROESY spectrum in CD_2Cl_2/CD_3OH. A diagnostic CH^{β}_{i}–NH_{i+3} cross peak is visible (Figure 3, circled in red), confirming the presence of a 3_{10}-helix along the structure of **9a**. The absence of CH_i–NH_{i+4} cross peak suggests that there is no α-helical contribution to the structure.



Scheme 3: Reagents and conditions: (a) DSC, DCM, rt; (b) 6,7-Dihydro-5H-dibenz[c,e]azepine hydrochloride, DIPEA, MeCN, rt. DSC = *N,N'*-Disuccinimidyl carbonate.

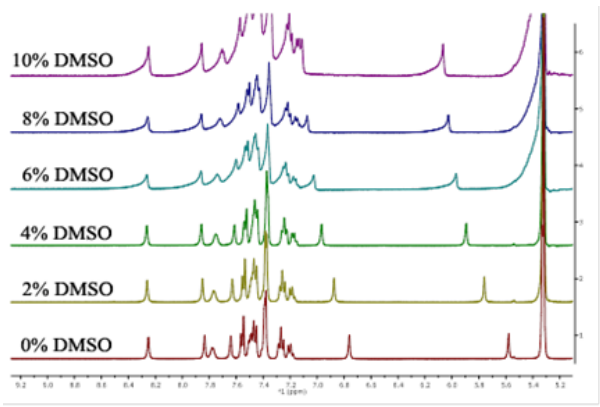


Figure 2: DMSO-d6 titration of **9a** (approx. 0.01 M in CD_2Cl_2/CD_3OH 9:1)

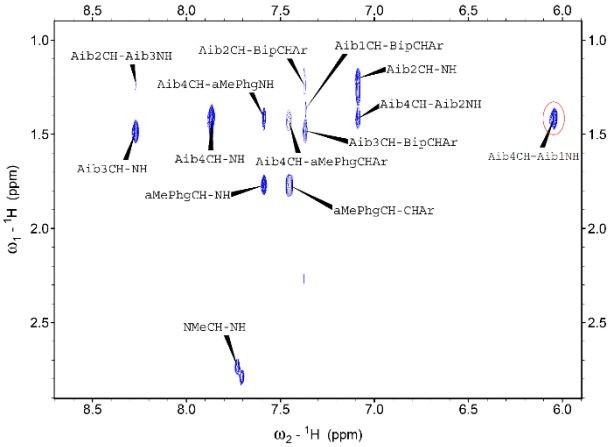


Figure 3: Aromatic region of the ROESY spectrum of **9a** (approx. 0.01 M in CD_2Cl_2/CD_3OH 9:1**).**

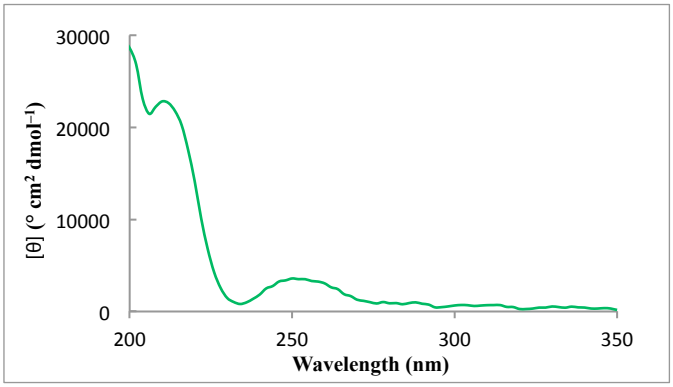


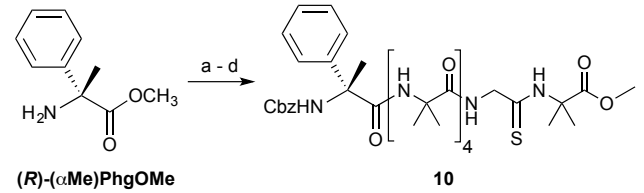
Figure 4: CD spectrum of **9a** (0.68 mM in MeOH)**.**

^{1}H NMR in CD_3OD revealed diastereotopic signals for the methylene groups of the azepine probe, indicating an excess of one screw-sense conformer over the other.[14] By comparison with the values obtained for other conformational controllers with known equilibrium ratios,[13a] we deduced that (*R*)-(αMe)Phg exhibits rather modest levels of control, with a helical excess (h.e.) of just 10% in a mixture of CD_3OH and $CDCl_3$ (9:1). The *ortho*-methoxy substituent of compound **9b** increases the control slightly to a h.e. of 21% in deuterated methanol.

The CD spectrum of peptide **9a** in methanol showed a local maximum centered around 250 nm for the biaryl probe (Figure 4). The molar ellipticity at this wavelength indicates a helical excess of about 7% induced at the probe (in line with the low value deduced by ^{1}H NMR spectroscopy), and its positive value indicates a right-handed (or *P*) screw-sense preference in solution. C-terminal amides of D-amino acids typically induce *M* helices whether the chiral residue is tertiary or quaternary,[12c] so this weak preference is opposite to that induced by related amino acids, presumably because of the unusual α-arylated structure of the controlling residue.

The effect of introducing **6a** at the *N*-terminus of the oligomer was explored using an Aib tetramer bearing a C-terminal thionoglycine probe (Scheme 4).[15] The methyl ester of **6a** was first capped with a carboxybenzyl (Cbz) protecting group and hydrolysed to the corresponding carboxylic acid. Tetramethylfluoroformamidinium hexafluorophosphate was used to form its acyl fluoride derivative, which was coupled to a hexamer already containing the embedded thioamide probe to afford foldamer **10**.

Variable Temperature ^{1}H NMR of peptide **10** in CD_3OH, between 5 and 35°C showed a significant downfield drift of the chemical shift of two of the amide protons. This suggests that only these two amide protons lie outside of the hydrogen-bonded network, consistent with the folding of **10** into a 3_{10} helix (Figure 5). In CD_3OD at room temperature, the foldamer shows a characteristic pair of signals for the diastereotopic methylene protons of the thionoglycine residue, centred around 4.20 ppm. Comparison of their anisochronicity with reported values[15] indicates that this N-terminal controller induces a helical excess of 42%, similar to that of L-CbzPhe.



Scheme 4: Reagents and conditions: (a) CbzCl, DIPEA, CH_2Cl_2, rt; (b) NaOH, MeOH, H_2O, rt; (c) TFFH, Pyridine, CH_2Cl_2, rt; (d) H-Aib$_4$Gly-ψ[CSNH]AibOMe, DIPEA, CH_2Cl_2, rt.

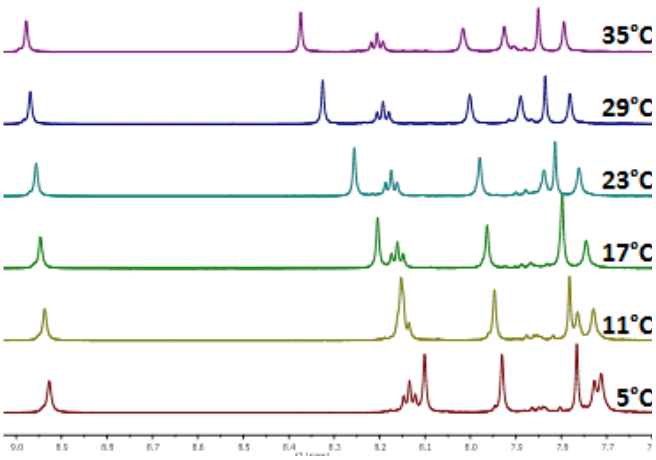


Figure 5: Variable Temperature ^{1}H NMR of **10** (approx. 0.01 M in CD_3OH).

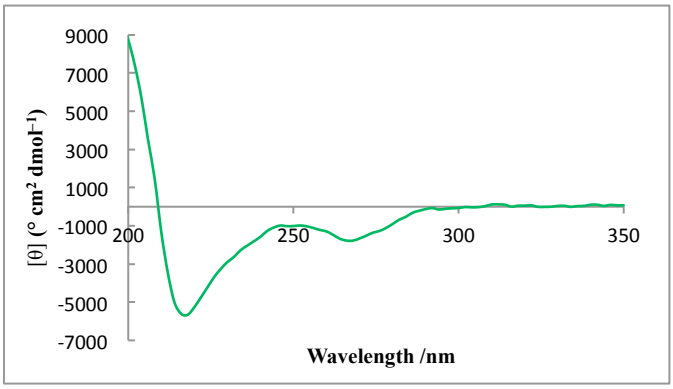


Figure 6: CD spectrum of **10** (0.62 mM in MeOH).

The CD spectrum of the foldamer shows the typical absorption band for the π-π* transition of the thionoglycine probe centered at 268 nm (Figure 6). The negative value of the ellipticity in this region indicates a left-handed screw-sense preference (or *M* helix) for compound **10**, indicating that, at this N terminus of the foldamer, (*R*)-(αMe)Phg induces the same screw-sense preference as the related quaternary amino acid (*R*)-(αMe)Val, presumably by the mechanism of induction previously proposed.[12,16,17]

Conclusions

Aryl substituents may be introduced enantioselectively to the α-carbon of alanine derivatives using the base-promoted rearrangement of a urea derivative carrying using pseudo-ephedrine as a chiral auxiliary. While migration of a phenyl ring occurs with excellent enantiomeric excess, other migrating rings showed low selectivity or low yield. Protection of the urea by 2,4-dimethoxybenzyl permits simple operational conditions, leading to quaternary arylated amino acids after deprotection and hydrolysis of the resulting hydantoin. Isolation of the opposite enantiomer to that obtained by a previously reported procedure[10] allows access to both enantiomers of the quaternary amino acid derivative by using the same chiral auxiliary.

(αMe)Phg **6a** (and its *ortho*-methoxylated derivative **6b**) participates in a 3_{10} helix when incorporated at either the N- or the C- terminus of an Aib oligomer. While these two unnatural amino acid derivatives induce moderate control over the overall screw-sense from the C-terminus**,** (αMe)Phg displays more promising levels of conformational control from the N-terminus.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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